PCT/IB 0 5 / 0 0 3 3 0

27. 04. 05

REC'D 27 APR 2005

WIPO PCT

Australian Government

Patent Office
Canberra

I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2004900661 for a patent by RUBICON RESEARCH PRIVATE LIMITED as filed on 11 February 2004.

WITNESS my hand this
Twenty-fourth day of January 2005

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

AUSTRALIA

PATENTS ACT 1990

PROVISIONAL SPECIFICATION

FOR THE INVENTION ENTITLED:-

"CONTROLLED RELEASE COMPOSITIONS WITH IMPROVED BIOAVAILABILITY"

The invention is described in the following statement:-

Controlled release compositions with improved bioavailability

Field of invention

The present invention relates to controlled release oral pharmaceutical compositions with improved bio-availability having at least one active pharmaceutical ingredient of low bioavailability owing to low aqueous solubility and/or limited absorption on oral administration.

The present invention particularly relates to a controlled release pharmaceutical composition having at least one active pharmaceutical ingredient of low bioavailability owing to low aqueous solubility and/or limited absorption where its bioavailability is improved by solubilizing the active ingredient using a solubilizer and incorporating it in a gastro-retentive system.

Prior Art

Controlled release dosage forms that provide prolonged delivery of active pharmaceutical ingredients have found application for increasing numbers of pharmaceutical ingredients. However, with respect to pharmaceutical and veterinary compositions, there has been a need not only to provide for prolonged delivery of the active agent over time, but also to provide prolonged delivery of the active agent at a particular location or locations in the environment of use, such as in the stomach or small intestines.

Certain active agents are absorbed primarily from the small intestine. Generally, the time of passage of different particles through the small intestine does not vary significantly, and passage is generally independent of food intake and particle size. Thus, active agent dissolved in liquid, solid active agent particles dispersed in liquid or relatively small delivery units of active agent, such as microcapsules and the like, will traverse the length of the small intestine in substantially the same time frame, usually about 3-5 hours. For active agents that are not easily absorbed by the small intestine or that do not dissolve readily, the window for active agent absorption in the small intestine may be too short to provide a desired therapeutic effect. This fact often creates a need for frequent dosing of large amount of active agent in order to provide and maintain adequate levels of active agent in blood plasma. The need for frequent dosing presents compliance problems and is often inconvenient for the user as well and the need for large amount of active ingredient may result in increased toxicity. This problem is further accentuated for active pharmaceutical agents having low aqueous solubility characteristics.

The need to increase the solubility of low solubility drugs in order to increase its bioavailability is long felt and attempts made in the prior art are described in some of the following patents.

1) US Patent, 5883103 Burnside, et al

Claims for oral aciclovir delivery comprising a stable, hydrophobic emulsion comprising continuous phase of a Hydrophobic material selected from the group of long chain carboxylic acid or esters or alcohol thereof dispersed in an aqueous phase or having a

hydrophilic discontinuous phase dispersed in a hydrophobic phase of a long chain carboxylic acid or alcohol thereof. The emulsion with aciclovir is incorporated into a pharmaceutical carrier suitable for oral delivery. Thus in this invention an emulsion of aciclovir is prepared which is a lengthy and critical process.

2) US Patent 5736161 by Garces ,et al

Describes a method and composition for improving the absorption of drug taken by the oral route by means of encapsulation in millispheres of gellable hydrocollids covered with positively charged polysaccharide.

3) US Patent 5472954 Loftsson and Thorsteinn

provides a method for enhancing the complexation of a cyclodextrin with a lipophilic and /or water-labile active ingredient.

As seen from the prior art, though various methods and attempts are made to increase the solubility of the low solubility drug, however there are a large number of constraints for increasing the solubility of drug, by many of these processes and difficulties are encountered to extend such processes to commercial scale manufacture.

A further review of prior art reveals that although several attempts were made to increase the solubility of sparingly soluble drugs (like aciclovir) by complexation, or preparation of microemulsion this concept was not utilized further to formulate a controlled release oral dosage form using it. It is thus noted from the prior art that the attempts for solubilizing low

solubility drugs were not further extended to formulate controlled release compositions of such solubilized drugs.

Attempts made in the prior art to achieve effective gastro-retentive, controlled release compositions are summarized in the following patents:

4) Patent 5780057 Connate, and Luaretta et al

Describes a pharmaceutical form for oral administration comprising of 2 or 3 layer tablets where at least one layer can rapidly swell by contact with biological and/ or aqueous fluids, said swelling resulting in a considerable increase in the tablet volume. This phenomenon determines a prolonged residence of the pharmaceutical dosage form at the gastric level and allows a slow release of the active ingredient from said pharmaceutical form to the stomach and/or the first tract of the intestines .

5) US Patent, 6117,453 Seth, et al

Relates to solid pharmaceutical composition, containing polyethylene oxide and an active ingredient like aciclovir, nifedipine, captropril etc and the method for the preparation of a controlled release formulation.

6) US Patent 6340475 Shell et al

Describes water soluble drug formulated as unit dosage form by incorporating it into polymeric matrices comprised of hydrophilic polymer that swell upon imbibing water, to a

size the is large enough to promote retention of the dosage form in the stomach during the fed mode.

7) US Patent 20030104052A- Berner, Bret et al

This patent details a controlled release oral dosage form to provide continuous and sustained administration of a pharmacologically active agent to the upper gastrointestinal tract of a patient in fed state. The dosage form comprises a matrix of a biocompatible hydrophilic, erodible polymer with an active agent incorporated in it. The release is due to simultaneous swelling & erosion of the polymer after coming in contact with the gastric fluid. The drug release rate is primarily controlled by the erosion rate.

8) US Patent 6120803 Wong et al

Describes compositions where the dosage form of the active agent is a polymer matrix that swells upon contact with fluid of stomach and a portion of the polymer matrix is surrounded by a band of insoluble material that prevents the concerned portion of polymer matrix from swelling and provides a segment of the dosage form that is of sufficient rigidity to with stand the environment of the stomach and delay expulsion of the dosage form from the stomach until substantially all of the active agent has been dispersed.

9) US Patent Autant et al

This patent relates to microcapsules for oral administration of medicinal and nutritional active principles which are smaller than 1000 μm and which are characterized by the ability

to remain in the small intestine for a long time (at least 5 hrs) and allow during this residence, release and absorption of the active principles.

10) US Patent 5972, 389 Shell; John W et al

This patent claims a controlled release oral dosage form for releasing a sparingly soluble drug into the stomach, duodenum and small intestine, comprising of solid particles consisting of said drug dispersed within a polymer, poly(ethylene oxide).

11) US Patent 6488962 Berner, Bret et al

Relates to the shape of tablets for enhancing gastric retention of a swellable controlled release oral dosage form and which prevents the tablets from inadvertently passing through the pylorus as a result of being in a particular orientation.

It is thus evident that many attempts were made in prior art to formulate controlled release compositions utilizing various techniques like increasing the size of the tablets after ingestion, or formation of a non- swellable band, or a bioadhesive composition, or preparation of microspheres that remain in the small intestine for 5 to 6 hrs, using various polymers and their combination but none of these include controlled release compositions of low bioavailability drugs whose instantaneous solubility is increased prior to controlling their release.

Thus there is a long felt need to combine the concepts of solubilising low solubility drugs and to formulation gastroretentive, controlled release compositions in order to effectively increase their bioavailability.

The present inventors have surprisingly found that compositions of sparingly soluble drugs having improved instantaneous solubility when formulated in a controlled release form achieve more than 80% drug release in 12 hrs in dissolution studies; this was not possible to attain when such drugs were available in either only solubilised compositions or only controlled release compositions as such.

Objects of the Invention

An object of the present invention is to provide controlled release pharmaceutical compositions for oral administration having at least one active pharmaceutical ingredient of low bioavailability due to low aqueous solubility and/or limited absorption in the gastrointestinal tract wherein its instantaneous solubility is increased prior to controlling its release.

Another object of the present invention is to solubilize low solubility drugs and further utilize the solubilized drugs to formulate controlled release compositions to effectively increase their bioavailability.

Yet another object of the present invention is to provide a simple and cost effective controlled release pharmaceutical composition, for improved bioavailability which would be simple to manufacture.

A further object of the present invention is to provide gastroretentive compositions that are retained in stomach for longer period of time thereby increasing the bioavailability of the drugs with limited absorption.

A further object of the present invention is to provide a controlled release pharmaceutical composition that has reduced level of dose frequency and therefore improved patient compliance.

Yet further object of the present invention is to combine solubilisation of drug with gastroretention to achieve controlled release of low solubility drug, improved bioavailability, reduction in dose level, reduction in dosage frequency, reduction in undesirable side effects and improved patient compliance.

Summary of invention:

Thus according to an aspect of the present invention there is provided a controlled release oral pharmaceutical composition comprising of:

a) therapeutically effective amount of one or more pharmacologically active agent having low bioavailability;

b) one or more solubilizers,

c) one or more biocompatible swelling agents, and

d) a swelling enhancer

wherein the swelling agent, in combination with swelling enhancer, swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide retention of the dosage form in the stomach of a patient, and gradually erode within the gastrointestinal tract over a prolonged time period.

Description of Invention: -

Controlled release of the drug with improved bioavailability, reduction in dose, reduction in dosage frequency, reduction in undesirable side effects and improved patient compliance are achieved by combining solubilisation of low solubility drugs with gastro-retention.

The present invention comprises the preparation and use of a solubilised low solubility drug in a sustained release, gastro-retentive system wherein the maximum amount of drug will be available for absorption by virtue of its solubilised property and continuous release through the gastro-retentive system.

The invention is particularly useful for drugs having a narrow window of absorption wherein the concept of gastro-retention employed allows a continuous trickling of the solubilised drug over the window of absorption, thus achieving controlled release and maximizing bioavailability of the drug. .

Accordingly the present invention provides for two essential components for formulating the controlled release composition:

1) ***Solubilisation of the drug***: - The low solubility drugs are solubilised using surface active agents like hydrophilic surfactants, lipophilic surfactants or mixtures thereof.

2) ***Gastro-retention of the drug***:- This solubilised drug is then incorporated in a gastro-retentive matrix system, which remains in the stomach by virtue of its size after swelling and allows a slow and continuous release of the solubilised drug which helps in increasing the extent of drug absorption and hence improves its bioavailability.

1. Solubilization of the drug:

According to this invention, the increase in instantaneous solubility of the drug is achieved by using suitable solubilizer.

The low solubility drug and solubilizer may be employed in different ratios. The selection of ratio depends upon the properties of the active ingredient, the desired improvement in its solubility and the type of the solubilizer employed.

For the purposes of this invention, the ratio of drug: solubilizer can range from 20 :1 to 1:20.

The preferred ratio of drug: solubilizer ranges from 10 :1 to 1 :10. The most preferred ratio being 5:1 to 1:5.

A combination of solubilizers may also be included wherein the total amount of solubilizer employed is maintained in the above-mentioned ratio.

Different non-limiting processes may be employed to prepare a solid solution of the drug and solubilizer or to form a physical mixture so as to increase the solubility of the active ingredient.

For example the processes may include solubilisation using melt granulation or solvent treatment method.

In case of melt granulation, the solubilizer is melted and the drug is added and mixed with the molten mass effectively, allowed to solidify and the granules are separated from each other. In another embodiment of this system the drug is granulated using molten solubilizer. In some cases drug and solubilizer both may be melted together and cooled to room temperature.

In case of using solvent treatment method, either the solubilizer or the drug, or both are dissolved in a solvent and the solvent is then evaporated. The resultant mass is a blend of drug and solubilizer, such that the solubility of the drug is increased. Solvent employed in this system may be aqueous or non-aqueous depending on the solubility of the drug and solubilizer.

A combination of hot melt process and solvent treatment method can also be employed. In this case the drug may be initially granulated with molten solubilizer which can be further treated with a same /different solubilizer in a solvent or vise versa.

Any process suitable for solubilisation of drugs may be employed for the purpose of this invention.

Melt granulation is the most preferred method for solubilisation of the drug, according to this invention. The increase in solubility can be determined by studying the actual solubility studies of the drug in presence of solubilizer or it can also be determined by carrying out dissolution studies in an appropriate dissolution medium. The dissolution method is preferred as it allows for calculation of the rate of dissolution by determining the amount of drug dissolved at different time intervals

2. Gastro-retention of the drug:

Second important component of the system comprises of the technology that allows gastro-retention. A number of gastro-retentive sustained release systems are reported in the literature. The following three major approaches describe gastroretentive controlled release devices that may be employed for the purpose of the invention: -

1) ***Floating or buoyant system:*** These are designed to have low density to enable them to float on gastric contents after their administration until the system either disintegrates, or the device absorbs fluid to the point where its density increases to an extent that it looses buoyancy and can then pass more easily from the stomach with a wave of motility that is responsible for gastric emptying.

2) ***Bioadhesive system***:- These are designed to imbibe fluid following their administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucous/ mucus layer.

3) ***Swelling and expanding system:*** - These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult, but on ingestion rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to the required degree.

Floating or buoyant systems require special techniques to decrease density of the dosage form or contain certain gas generating agent. These systems therefore are larger in size and do not allow use of high dosages of drugs. It is difficult to achieve bioadhesion in the gastric mucosa due to the large amount of fluid present in the stomach and also the gastric motility through the housekeeper wave that causes dislodgement of the dosage form. The most successful approach for gastro retention is the swelling and expanding system. A swelling and expanding system is employed in the present invention. However the other two approaches for gastro-retention, namely floating and bioadhesive system are also suitable for use

According to the present invention, a controlled release, gastro-retentive swelling system incorporating solubilised drug is described.

The controlled release gastro-retentive swelling system of the present invention employs a combination of polymers, which swell voluminously in presence of gastric contents to increase the dosage form size such that it precludes its passage through the pylorus.

The present inventors have surprisingly found that addition of swelling enhancers to the gastro-retentive swelling system reduces the swelling time considerably which can further aids in improving bio-availability of drugs with narrow absorption window.

The dosage form of the present invention is a solid dosage form, preferably a tablet, which may vary in shape, such as oval, triangle, almond, peanut, parallelogram, pentagonal.

The preferred shapes are oval and parallelogram forms.

Tablets in accordance with this invention using a solubilised drug in a controlled release gastro retentive dosage form may be manufactured using the conventional techniques of common tableting methods like:

1) Direct compression
2) Wet granulation
3) Dry granulation
4) Extrusion/ melt granulation

When the dosage form is in the form of tablets , additional excipients conventionally known in art such as filler, binders and lubricants may be incorporated. Fillers such as lactose monohydrate, microcrystalline cellulose, Dicalcium phosphate may be used, Binder like

polyvinyl pyrolidone, lubricants like Aerosil-200, Magnesium stearate and hydrogenated vegetable & triglycerides of stearic acid, palmitic acid may be utilized.

In one of the embodiments of the present invention, the composition may optionally be coated. Surface coating may be employed for aesthetic purposes or for dimensionally stabilizing the compressed tablet. The coating may be any conventional coating which is suitable for enteral use. The coating may be carried out using any conventional technique employing conventional ingredients. A surface coating can for example be obtained using a quick-dissolving film using conventional polymers such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, polyvinyl alcohol poly methacrylates and the like.

The tablet after ingestion gradually swells upon contact with water (and hence gastric fluid) The time taken for swelling may vary from 15 min to 4 hours preferably within 15 min to 3 hours and most preferably within 15min to 2 hrs.

The shorter axis of the tablets has to expand to a length of more than 0.8 cm, preferably more than 1.0 cm.

The controlled release compositions of the present invention comprise

a) therapeutically effective amount of one or more pharmacologically active agents having low bioavailability;

b) one or more solubilizers,

c) one or more biocompatible swelling agents, and

d) a swelling enhancer

wherein the swelling agent in combination with swelling enhancer swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide gastric retention of the dosage form in the stomach of a patient; and gradually erodes within the gastrointestinal tract over a prolonged time period.

Pharmacologically active agent:

The pharmacologically active agents for the purpose of this invention are those having low bioavailability. This low bioavailability could be because of low solubility and/or limited oral absorption or a narrow absorption window. The active agents may be selected from one of the following therapeutic classes of active substances that includes: antiulcer, antidiabetic, anticoagulant, antithrombic, hypolipaemic, antiarrhythmic, vasodilatory, antianginal, antihypertensive, and vasoprotective agents, fertility enhancers, labour inducers and inhibitors, and contraceptive, antibiotic, antifingal, antiviral, anticancer, anti-inflammatory, analgesic, antiepileptic, antiparkinsonian, neuroleptic, hypnotic, anxiolytic, psychostimulatory, antimigraine, antidepressant, antitussive, antihistamine or antiallergic agents.

The active agents may be selected from pentoxifyllin, prazosin, aciclovir, levodopa, nifedipin, diltiazem, naproxen, flurbiprofen, ketoprofen, fenoprofen, fentiazac, oestradiol valerate, metoprolol, sulpiride, captopril, cimetidin, zidovudin, nicardipine, terfenadine,

salbutamol, carbamazepin, ranitidine, enalapril, simvastatin, fluoxetin, famotidin, ganciclovir, famiciclovir, valaciclovir ciprofloxacin pentazocin, omeprazol, saguinavir, ritonavir, nelfinavir, thiamphenicol, clarithromycin, azithromycin, ceftazidime, cyclosporin, digoxin, paclitaxel, iron salts, eprosartan, losartan potassium, valsartan, candesartan, topiramate, and ketoconazole etc and mixtures thereof.

Solubilizer:

In accordance to the features of the present invention, the solubilizer acts to increase the instantaneous solubility of the pharmaceutically active agent.

The solubilizer may be selected from hydrophilic surfactants or lipophilic surfactants or mixtures thereof.

The surfactants may be anionic, nonionic, cationic, and zwitterionic surfactants.

The hydrophilic non-ionic surfactants may be selected from the group comprising of polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils preferably glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide,

The ionic surfactants may be selected from the group comprising of alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

The lipophilic surfactants may be selected from the group comprising of fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; PEG sorbitan fatty acid esters, PEG glycerol fatty acid esters, polyglycerized fatty acid, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters; and mixtures thereof.

Preferably the solubilizer may be selected from PEG-20-glyceryl stearate (Capmul® by Abitec), PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), PEG 6 corn oil (Labrafil® by Gattefosse), lauryl macrogol – 32 glyceride (Gelucire 44/14® by Gattefosse) stearoyl macrogol glyceride (Gelucire 50/13® by Gattefosse), polyglyceryl – 10 mono dioleate (Caprol ® PEG 860 by Abitec), propylene glycol oleate (Lutrol ® by BASF), Propylene glycol dioctanoate (Captex® by Abitec)Propylene glycol caprylate/caprate (Labrafac® by Gattefosse), Glyceryl monooleate (Peceol® by Gattefosse), Glycerol monolinoleate (Maisine ® by Gattefosse), Glycerol monostearate (Capmul® by Abitec), PEG- 20 sorbitan monolaurate (Tween 20® by ICI), PEG – 4 lauryl ether (Brij 30® by ICI), Sucrose distearate (Sucroester 7® by Gattefosse), Sucrose monopalmitate (Sucroester 15® by Gattefosse), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series

BASF), polyethylene glycol 660 hydroxystearate, (Solutol® by BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, Proylene glycol alginate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, betains , polyethylene glycol (Carbowax® by DOW) etc.

The most preferred solubilizer may be selected from PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), lauryl macrogol – 32 glyceride (Gelucire 44/14® by Gattefosse) stearoyl macrogol glyceride (Gelucire 50/13® by Gattefosse), PEG- 20 sorbitan monolaurate (Tween 20® by ICI), PEG – 4 lauryl ether (Brij 30® by ICI), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, polyethylene glycol (Carbowax® by DOW) etc.

Biocompatible swelling agent:

The swelling agent used in the present invention includes one or more swellable biocompatible hydrophilic polymers. Preferably, the polymers are employed in the dry state or in a form that has substantial capacity for water uptake.

Water-soluble polymers useful in preparation of the said composition of this invention includes polymers that are nontoxic and that swell in a dimensionally unrestricted manner upon imbibition of water and hence gastric fluid. Examples of polymers which can be used are polyalkylene oxides; cellulosic polymers; acrylic acid and methacrylic acid polymers, and esters thereof, maleic anhydride polymers; polymaleic acid; poly(acrylamides);

poly(olefinic alcohol)s; poly(N-vinyl lactams); polyols; polyoxyethylated saccharides; polyoxazolines; polyvinylamines; polyvinylacetates; polyimines; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; zein; shellac-based polymers; polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid, maltodextrin, pre-gelatinized starch and polyvinyl alcohol and copolymers and mixtures thereof.

One or more hydrophilic polymers is preferably selected from the group consisting of polyethylene oxide, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxy methylcellulose, calcium carboxymethyl cellulose, methyl cellulose, polyacrylic acid, maltodextrin, pre-gelatinized starch and polyvinyl alcohol.

The hydrophilic polymer is more preferably a polyalkylene oxide selected from the group consisting of poly(ethylene oxide), poly(ethylene oxide-co-propylene oxide), and mixtures thereof.

The hydrophilic polymer is most preferably poly(ethylene oxide).

At least one of the biocompatible hydrophilic polymer has a number average molecular weight in the range of approximately 5,000 and 20,000,000.

The weight percent of the hydrophilic polymer in the dosage form is about 5 to 90 weight percent, preferably about 10 to 70 weight percent, and most preferably about 15 to 50 weight percent.

Swelling enhancers:

Swelling enhancer is a member of a special category of excipients that swell rapidly to a large extent resulting in a dramatic increase in the size of the tablet. At lower concentrations, these excipients are used as superdisintegrants; however at concentration above 5 % w/w these agents function as swelling enhancers and help to increase the size of the tablet.

The examples of swelling enhancers include low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal magnesium-aluminum silicate, corn starch granules, rice starch granules, potato starch granules, pregelatinised starch and sodium carboxymethyl starch.

The swelling enhancer is preferably cross-linked polyvinyl pyrrolidone. The content of the swelling enhancer is about 5 to 90 weight percent preferably about 10 to 70 weight percent, most preferably about 15 to 50 weight percent.

The composition of the present invention may make use of a single polymer alone or combination of polymers with or without a swelling enhancer as required.

When a combination of polymers and swelling enhancer is employed for gastro-retention, the swelling enhancer would allow a rapid and dramatic increase in the size of the tablets. However,the swelling enhancer itself alone by themselves cannot maintain the integrity of the dosage form and avoid its disintegration.

On the other hand,the polymers may not show the rapid increase in size desired for gastro-retention by themselves alone due to their slow rate of swelling.

Therefore, a synergistic combination may preferably be employed which allows rapid swelling by virtue of the presence of swelling enhancer and maintenance of integrity by polymeric network formed by swelling of the polymer(s).

Thus the invention describes a unique combination of technologies wherein a solubilised drug is incorporated into a swelling matrix of polymer(s) and swelling enhancer to achieve gastro-retention. Controlled release is thus achieved by; integrity of the matrix and the need for the gastric fluid to diffuse into the matrix or is achieved by controlled rate of erosion of the matrix, and the need for the matrix to erode in order to release much of the drug or a combination of the two.

The gastro-retentive controlled release compositions of the present invention that include a solubilized drug find utility when administered to patients in the fed or the fasting mode. The fed mode is preferred since the narrowing of the pyloric opening that occurs in the fed mode serves as a further means of promoting gastric retention by retaining a broader range of size of the dosage form . Following oral administration to a patient, the dosage form is retained in the upper gastrointestinal tract for a time period of about 30 min to 12 hours or 1 to 9 hours or most preferably 1to 6 hours.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to non-limiting exemplary illustrations

Example 1:

Swelling studies:

In these studies various polymer placebo tablets were prepared at a polymer concentration of 20% w/w and the rate of swelling was determined in 0.1N HCl

Sr. No	Polymers	Swelling in 50 ml 0.1 N HCl				
		15 min	1 Hrs	2 Hrs	3 Hrs	4 hrs
1.	Xanthum Gum	18.8x 8 mm	20x10mm	21x11mm	21x12mm	21x12mm
2.	Polyoxyethylene WSR 1105	18.8x 8 mm	20x10mm	21x11 mm with slight erosion	21x12mm with slight erosion	21x12 mm with erosion
3.	Polyoxyethylene WSR N 60 K	18.8x 8 mm	20x10mm	21x12 mm	21x13 mm	21x13 mm
4.	Polyoxyethylene WSR 301	18.8x 8 mm	20x10mm	21x12 mm	21x12 mm	21x13 mm
5.	Methocel K100	18.8x 8 mm	19x9 mm	20x10 mm	21x11 mm	22x12 mm
6.	Methocel K100 M	18.8x 8 mm	19x9 mm	20x10 mm	21x11 mm	22x12 mm
7.	Methocel K4M	18.8x 8 mm	19x10 mm	20x10 mm	21x11 mm	22x12 mm

The study showed that,among various polymers studied the polyoxyethylenes exhibit maximum rate of swelling. Although, these polymers alone can be used for gastro-retentive drug delivery systems, there is a need to further increase the rate of swelling.

Example 2:

In this example swelling enhancers, namely crospovidone, crosscarmellose sodium, sodium starch glycolate and starch 1500, were incorporated into a placebo tablet at a concentration of 10% w/w. However these agents resulted in too rapid and voluminous swelling of the dosage forms leading to their disintegration.

Example 3:

A combination of swelling enhancer and a matrix forming polymer was incorporated in a placebo tablet. The following table gives the rates of swelling of these dosage forms.

Sr. No.	Polymer / swelling enhancer	15 min	60 min	120 min
1	Polyoxyethylene 60 K/ Crospovidone (1:1.5)	18.8x 8 mm	22 x12 mm with erosion	22 x13 mm with erosion
2	Polyoxyethylene 60 K /Crospovidone (1:1)	18.8x 8 mm	22 x13 mm with slight erosion	22 x13 mm with slight erosion
3	Polyoxyethylene 60 K/ Crospovidone (1.5:1)	18.8x 8 mm	22 x13 mm with slight erosion	22 x13 mm with slight erosion
4	Methocel K100 M/ Crospovidone (1.5 :1)	18.8x 8 mm	20 x 10 mm	21 x 11 mm
5	Methocel K4M / Crospovidone (1.5 :1)	18.8x 8 mm	20 x 11 mm	22 x 11 mm

The above example show that combination of swelling enhancer and polymer results in tablets with a faster rate of swelling,as desired for gastro-retention.

Example 4:

Solubilization of drug using various solubilizing agents:

The solublizing agent is melted in a container and to it the drug was added and mixed intimately and cooled to room temperature. The mass was sifted through an appropriate sieve to get a uniform blend. Blend of the drug were prepared using polyethylene glycol 6000, Lutrol F127 and Gelucire (50/13) Solid dispersion of the drug with various solubilizing agents like polyethylene glycol 6000, Lutrol F127 and Gelucire 50/13 were studied for its solubility in 900 ml distilled water.

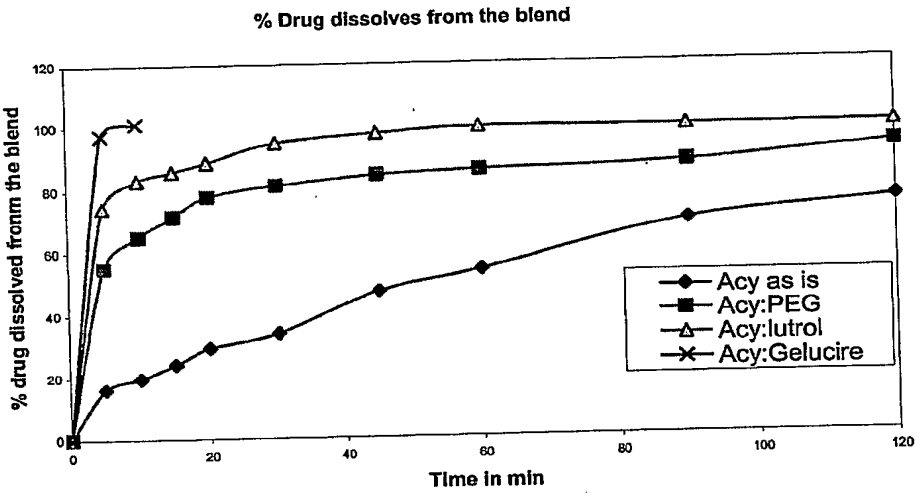
Aciclovir in a ratio of (1:1 and 1:5) with polyethylene glycol 6000 showed a two-fold increase in solubility, aciclovir in ratio of (1:0.5 to 1:1) with Gelucire 50/13 showed a 5 fold increase in instantaneous solubility against aciclovir as such.

Also with Lutrol in ratio (1:0.5 to 1:2) a three-fold increase in instantaneous solubility was observed.

The result obtained are provided in Table I hereunder and graphically represented by Figure-I:

Table I:

Time in min	Aciclovir as is (% drug dissolved)	Aciclovir :PEG (% drug dissolved)	Aciclovir : Lutrol (% drug dissolved)	Aciclovir : Gelucire %dissolved
0	0	0	0	0
5	16.03	55.38	74.34	97.25
10	19.58	64.79	83.16	100.96
15	24.09	71.46	85.77	
20	29.34	77.85	88.49	
30	33.89	81.32	94.57	
45	47.11	84.30	97.22	
60	53.78	85.64	99.06	
90	68.87	87.45	98.86	
120	75.40	92.67	99.13	



As would be evident from the above data, we may conclude that use of solubilizing agents increases the instantaneous solubility of the low-solubility drugs like Aciclovir.

Example 5:

The solubilised drug was further used for formulating the controlled release tablets.

Based on the solubility data it was decided to use the combination of Aciclovir : Gelucire 50 /13 for the preparation of the tablets.

Ingredients	Mg/tablet	Mg/tablet
Aciclovir	250.00	250.00
Gelucire 50/13®	50.00	-
Polyoxyethylene WSR 60K	300.00	300.00

Crospovidone	350.00	350.00
Polyvinyl pyrrolidone K30 (PVP K30)	50.00	50.00
Magnesium stearate	10.00	10.00

Gelucire was melted and aciclovir was granulated with molten gelucire. These granules of aciclovir were further granulated with polymers using PVP K30. Granules were dried and lubricated and further compressed into tablets using a compression machine.

5

Dissolution condition:

I. Dissolution medium : 0.1N HCl

Volume of the dissolution medium : 900 ml

Temperature : 37°C

The results obtained are represented hereunder in Table III and graphically represented by Figure-II:

Table III:

Time intervals (hr)	Tablet with solubilised drug	Tablet with unsolubilised drug
0	0.00	0.00
2	20.89	30.95
4	36.90	43.57
8	66.73	63.39
10	84.59	69.72
12	97.04	75.81
14	-	78.04

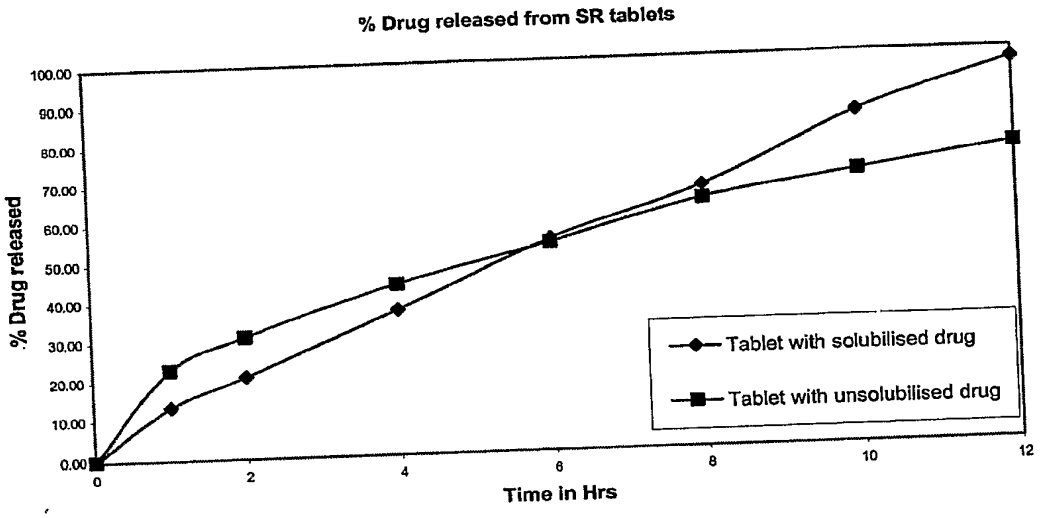


Figure II

5

Dated this 11th Day of February 2004